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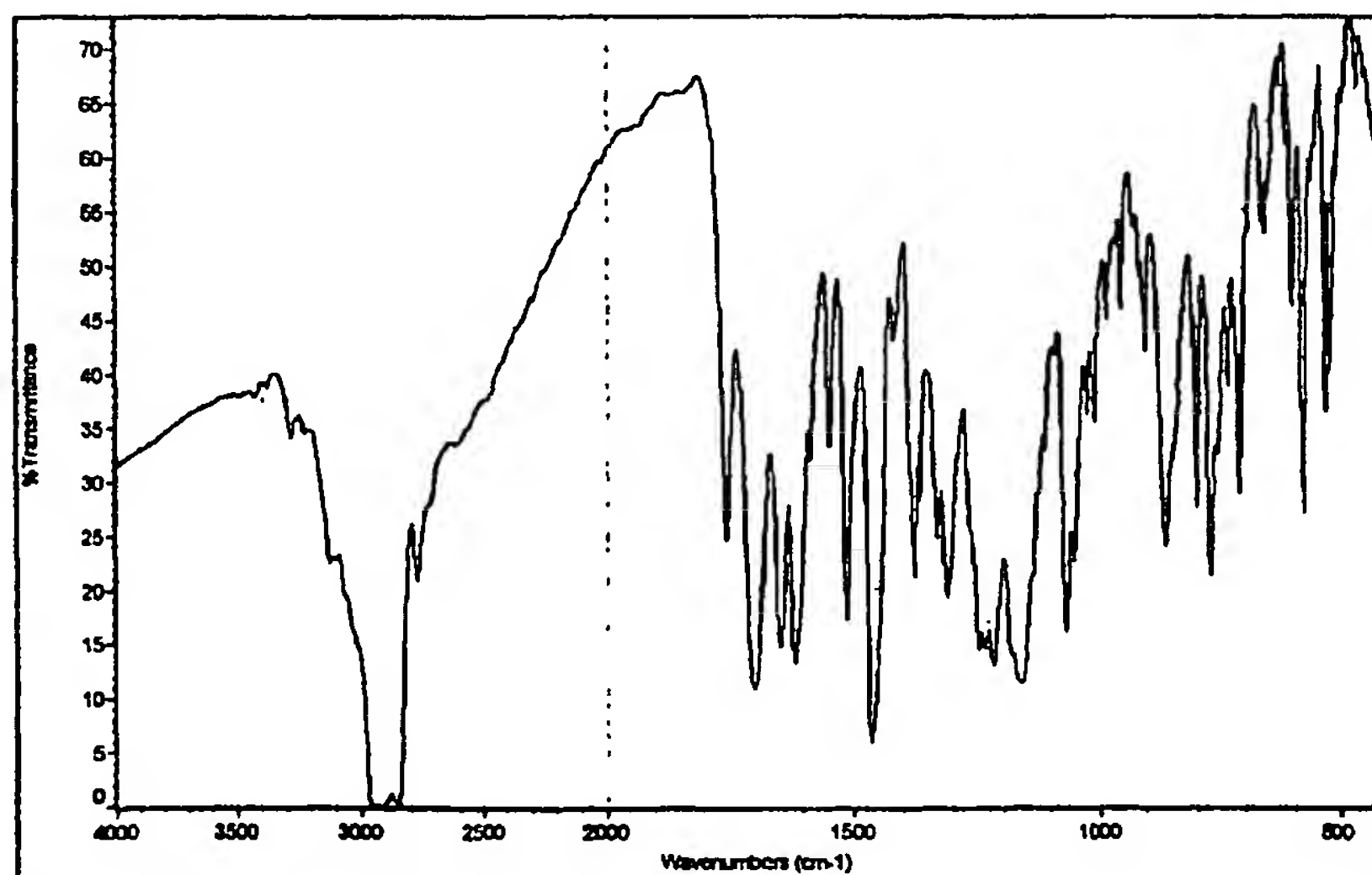
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(54) Title: HYDROGENSULFATE SALT OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE

Infrared spectrum of the Hydrogensulfate



(57) Abstract: A 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt, a process for preparing such a salt, a pharmaceutical composition containing such as salt and the use of such a salt in medicine.

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## HYDROGENSULFATE SALT OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

5 EP-A-0 306 228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of Example 30 of EP-A-0 306 228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter referred to as "Compound (I)").

10 WO 94/05659 discloses certain salts of the compounds of EP-A-0 306 228. The preferred salt of WO 94/05659 is the maleic acid salt. Sulfuric acid is mentioned as a favoured, pharmaceutically acceptable acid source of a potential counter-ion for salt formation. The preparation of a sulfuric acid salt is not exemplified.

There remains a need for alternative salt forms which have properties suitable for pharmaceutical processing on a commercial scale.

15 We have now prepared and characterised a hydrogensulfate salt of Compound (I) (hereinafter also referred as the "Hydrogensulfate") that is particularly stable and hence suitable for bulk preparation and handling.

The novel salt can be prepared by an efficient and economic process particularly suited to large-scale preparation. The Hydrogensulfate is a stable, high melting  
20 crystalline material hence is suitable for bulk preparation and handling. The Hydrogensulfate is amenable to large scale pharmaceutical processing, especially in manufacturing processes which require or generate heat, for example milling, fluid bed drying, spray drying, hot melt processing and sterilisation by autoclaving. The novel salt can be prepared by an efficient, economic and reproducible process particularly suited to  
25 large-scale preparation.

The Hydrogensulfate also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

30 Accordingly, the present invention provides a 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt.

The Hydrogensulfate is formed from one molecule of Compound (I) and one molecule of sulfuric acid. The Hydrogensulfate consists of one molecule of Compound (I) in appropriate ionic form and one hydrogensulfate anion. An appropriate ionic form is a protonated form. An appropriate ionic form is a cationic form. Thus the  
35 Hydrogensulfate is a (1:1) salt of Compound (I), generally in a cationic form, and the  $\text{HSO}_4^-$  ion. The Hydrogensulfate is therefore conveniently represented by the formula

MHS wherein M is a cationic form of Compound (I) and HS is a hydrogensulfate anion ( $\text{HSO}_4^-$ ).

5 This invention also envisages a mixed salt of Compound (I) and the  $\text{SO}_4^{2-}$  ion of formula MSN wherein M is a cationic form of Compound (I), S is a sulfate cation ( $\text{SO}_4^{2-}$ ) and N is an alternative cation such as an alkali metal or ammonium cation. In one favoured aspect, the Hydrogensulfate provides an infrared spectrum substantially in accordance with Figure 1.

In one favoured aspect, the Hydrogensulfate provides a Raman spectrum substantially in accordance with Figure 2.

10 In one favoured aspect, the Hydrogensulfate provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3.

In one favoured aspect, the Hydrogensulfate provides a Solid State  $^{13}\text{C}$  NMR spectrum substantially in accordance with Figure 4.

15 In a preferred aspect, the invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt, characterised in that it provides:

- (i) an infrared spectrum substantially in accordance with Figure 1; and
- (ii) a Raman spectrum substantially in accordance with Figure 2; and
- (iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table
- 20 1 or Figure 3; and
- (iv) a Solid State  $^{13}\text{C}$  NMR spectrum substantially in accordance with Figure 4.

The present invention encompasses the Hydrogensulfate or a solvate thereof isolated in pure form or as a mixture with other materials.

25 Thus in one aspect there is provided the Hydrogensulfate or a solvate thereof in isolated form.

In a further aspect there is provided the Hydrogensulfate or a solvate thereof in substantially pure form.

In yet a further aspect there is provided the Hydrogensulfate or a solvate thereof in crystalline form.

30 Also, the invention provides the Hydrogensulfate or solvate thereof in a solid pharmaceutically acceptable form, such as a solid dosage form, especially when adapted for oral administration.

Moreover, the invention also provides the Hydrogensulfate, or a solvate thereof, in a pharmaceutically acceptable form, especially in bulk form, such form being

35 particularly capable of pharmaceutical processing, especially in manufacturing processes which require or generate heat.

Examples of manufacturing processes which require or generate heat include milling, heat-drying especially fluid-bed drying, spray drying or hot melt processing and heat-sterilisation such as autoclaving. Particular examples of manufacturing processes which require or generate heat include milling, heat-drying especially fluid-bed drying, spray drying and heat-sterilisation such as autoclaving.

Furthermore, the invention provides the Hydrogensulfate, or a solvate thereof, in a pharmaceutically acceptable form, especially in a bulk form and especially in a form having been processed in a manufacturing process requiring or generating heat, for example in a milled form; for example in a heat-dried form, especially a fluid-bed dried form or a spray dried form; for example in a form having been hot melt processed; for example in a form having been heat-sterilised by such as autoclaving.

Suitable texts describing the manufacturing processes referred to herein include "The Theory and Practice of Industrial Pharmacy" edited by Leon Lachman, Herbert A. Lieberman and Joseph L. Kanig, published by Lea & Febiger and for spray drying and fluid bed drying Advanced Drying Technologies by Kudra, Tadeusz.; Mujumdar, A. S, New York Marcel Dekker, Inc., 2001.

The invention also provides a process for preparing the Hydrogensulfate or a solvate thereof, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)) or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a suitable source of hydrogensulfate ion; and optionally thereafter as required:

- (i) forming a solvate thereof;
- (ii) recovering the Hydrogensulfate or solvate thereof ; or
- (iii) further processing the Hydrogensulfate or solvate thereof in a manufacturing process requiring or generating heat.

A suitable reaction solvent is a ketone, for example acetone, or a hydrocarbon, such as toluene, an alkanol, such as propan-2-ol, an ester, such as ethyl acetate, an ether such as tetrahydrofuran, a nitrile such as acetonitrile, or a halogenated hydrocarbon such as dichloromethane or water ; or a mixture thereof.

Conveniently, the source of hydrogensulfate ion is sulfuric acid which may be concentrated or in diluted form. The sulfuric acid may be optionally further diluted with miscible organic solvent. For example, concentrated sulfuric acid may be added to a solution of Compound (I) in acetone.

An alternative source of hydrogensulfate ion is provided by a base salt of sulfuric acid for example ammonium hydrogensulfate, or the sulfuric acid salt of an amine, for example ethylamine or diethylamine.



Suitably the hydrogensulfate may be prepared by contacting stoichiometric amounts of the acid and Compound (I), or alternatively an excess of the acid may be used.

5 The concentration of Compound (I) is preferably in the range 3 to 50% weight/volume, more preferably in the range 5 to 20%. The concentration of sulfuric acid solutions are preferably in the range of 1 to 18 Molar.

The reaction is usually carried out at ambient temperature or at an elevated temperature, for example at the reflux temperature of the solvent, although any convenient temperature that provides the required product may be employed.

10 As indicated above the Hydrogensulfate can exist as a solvate. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates.

Solvates, such as hydrates, of the Hydrogensulfate may be prepared according to conventional procedures, for example by crystallising or recrystallising from a solvent which provides or contains the solvate moiety, or by exposing the Hydrogensulfate to the  
15 solvate moiety as a vapour. When a solvate is formed by crystallisation methods the nature of the solvate is typically dictated by the solvent from which the Hydrogensulfate is crystallised.

A salt of the abovementioned formula MSN is conveniently formed by reacting the Hydrogensulfate with a solution of the chosen monovalent salting ion N, for example  
20 a metal or ammonium ion. Alternatively a salt of the formula MSN is conveniently formed by reacting Compound (I), preferably dispersed or dissolved in a suitable solvent, with a compound of the formula  $MHSO_4$ , where M is, for example a metal or ammonium ion. Recovery of the required compound generally comprises crystallisation from an appropriate solvent, conveniently the reaction solvent, usually assisted by cooling. For  
25 example, the Hydrogensulfate may be crystallised from a ketone such as acetone or a hydrocarbon such as toluene. An improved yield of the salt may also be obtained by evaporation of some or all of the solvent or by crystallisation at elevated temperature followed by controlled cooling. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the product form.

30 Crystallisation can also be initiated by seeding with crystals of the Hydrogensulfate or a solvate thereof but this is not essential.

Suitable manufacturing processes requiring or generating heat include milling, heat-drying, especially a fluid-bed drying, hot melt processing or heat-sterilisation, such as autoclaving. Suitable manufacturing processes requiring or generating heat include  
35 milling, heat-drying, especially a fluid-bed drying or heat-sterilisation, such as autoclaving.

Compound (I) is prepared according to known procedures, such as those disclosed in EP-A-0 306 228 and WO 94/05659. The disclosures of EP-A-0 306 228 and WO 94/05659 are incorporated herein by reference.

Sulfuric acid is a commercially available compound.

5 When used herein the term "T<sub>onset</sub>" is generally determined by Differential Scanning Calorimetry and has a meaning generally understood in the art, as for example expressed in "Pharmaceutical Thermal Analysis, Techniques and Applications", Ford and Timmins, 1989 as "The temperature corresponding to the intersection of the pre-transition baseline with the extrapolated leading edge of the transition".

10 When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

15 Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes  
20 include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

25 As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly provides the Hydrogensulfate or a solvate thereof for use as an active therapeutic substance.

More particularly, the present invention provides the Hydrogensulfate or a solvate thereof for use in the treatment and/or prophylaxis of diabetes mellitus, conditions  
30 associated with diabetes mellitus and certain complications thereof.

The Hydrogensulfate or a solvate thereof may be administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. Suitable methods for formulating the Hydrogensulfate or a pharmaceutically acceptable solvate thereof are generally those disclosed for Compound  
35 (I) in the above mentioned publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Hydrogensulfate or a pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier therefor.

5 The Hydrogensulfate or a solvate thereof is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend  
10 on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices.  
15 Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets  
20 may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl  
25 hydrogensulfate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

30 Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose,  
35 aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of



glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Hydrogensulfate or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In a further aspect the present invention provides the use of Hydrogensulfate or a pharmaceutically acceptable solvate thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Hydrogensulfate or a pharmaceutically acceptable solvate thereof may be taken in amounts so as to provide Compound (I) in suitable doses, such as those disclosed in EP 0,306,228, WO94/05659 or WO98/55122.

The unit dose compositions of the invention comprise the Hydrogensulfate or a pharmaceutically acceptable solvate thereof in an amount providing up to 12 mg,

including 1-12 mg such as 2-12 mg of Compound (I), especially 2-4 mg, 4-8 mg or 8-12 mg of Compound (I), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I). Thus in particular there is provided a pharmaceutical composition comprising the Hydrogensulfate or a pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier thereof, wherein the Hydrogensulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 1, 2, 4, 8, 12, 4 to 8 or 8 to 12 mg of Compound (I); such as 1 mg of Compound (I); such as 2 mg of Compound (I); such as 4 mg of Compound (I); such as 8 mg of Compound (I); such as 12 mg of Compound (I).

The invention also provides a pharmaceutical composition comprising the Hydrogensulfate or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents and optionally a pharmaceutically acceptable carrier therefor.

The invention also provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Hydrogensulfate or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents.

In a further aspect the present invention provides the use of the Hydrogensulfate or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the above mentioned treatments the administration of the Hydrogensulfate or a pharmaceutically acceptable solvate thereof and the other anti-diabetic agent or agents includes co-administration or sequential administration of the active agents.

Suitably in the above mentioned compositions, including unit doses, or treatments the Hydrogensulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing up to 12 mg, including 1-12 mg, such as 2-12 mg of Compound (I), especially 2-4 mg, 4-8 mg or 8-12 mg of Compound (I), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 mg of Compound (I) or 4 to 8 or 8 to 12 mg of Compound (I). Thus for example in the above mentioned compositions, including unit doses, or treatments the Hydrogensulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 1 mg of Compound (I); the Hydrogensulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 2 mg of Compound (I); the Hydrogensulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 3 mg of Compound (I); the Hydrogensulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 4 mg of Compound (I); or the

Hydrogensulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 8 mg of Compound (I).

5 The other antidiabetic agents are suitably selected from biguanides, sulfonylureas and alpha glucosidase inhibitors. The other antidiabetic agent is suitably a biguanide. The other antidiabetic agent is suitably a sulfonylureas. The other antidiabetic agent is suitably a alpha glucosidase inhibitor. Suitable antidiabetic agents are those disclosed in WO98/57649, WO98/57634, WO98/57635, WO98/57636, WO99/03477, WO99/03476. The contents of the above mentioned publications are incorporated herein by reference as if set out in full herein.

10 No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following examples illustrate the invention but do not limit it in any way.

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**Example 1: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate**

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (3.0 g) in acetone (100 ml) was heated at reflux until a clear solution was observed. Concentrated sulfuric acid (0.47 ml) was added, and the reaction mixture stirred for 15 minutes at reflux, then cooled to 21°C. The product was collected by filtration, washed with acetone (20 ml) then dried under vacuum for 16 hours at 20°C to provide 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate (3.8 g) as a crystalline solid.

DSC:  $T_{\text{onset}} = 183.4^{\circ}\text{C}$ ,  $T_{\text{peak}} = 188.1^{\circ}\text{C}$

**Elemental Analysis:**

Found:	C; 47.25	H; 4.67	N; 8.99	S; 13.83
Theory: (C <sub>18</sub> H <sub>21</sub> N <sub>3</sub> O <sub>7</sub> S <sub>2</sub> )	C; 47.25	H; 5.07	N; 9.18	S; 14.02

**Example 2: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate**

Concentrated sulfuric acid (3.1 ml) was added to a stirred suspension of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (20.0 g) in acetone (300 ml) at reflux. The mixture was stirred for 1 hour at reflux, then cooled to 21°C. The white solid was collected by filtration, washed with acetone (100 ml) then dried under vacuum over phosphorus pentoxide for 48 hours to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate (25.1 g) as a white crystalline solid.

**Characterising data recorded for the product of Example 1:**

The infrared absorption spectrum of a mineral oil dispersion of the product was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm<sup>-1</sup> resolution (Figure 1). Data were digitised at 1 cm<sup>-1</sup> intervals. Bands were observed at: 2906, 2779, 1753, 1697, 1644, 1617, 1584, 1546, 1513, 1465, 1419, 1377, 1366, 1332, 1314, 1222, 1164, 1070, 1054, 1029, 1012, 988, 957, 906, 865, 801, 773, 736, 714, 663, 619, 604, 581, 532, 522, 433 cm<sup>-1</sup>.

The infrared spectrum of the solid product was recorded using Perkin-Elmer Spectrum One FT-IR spectrometer fitted with a universal ATR accessory. Bands were observed at: 2980, 2778, 1753, 1693, 1644, 1616, 1547, 1513, 1466, 1442, 1418, 1388, 1366, 1313, 1219, 1160, 1069, 1053, 1029, 1012, 988, 957, 906, 862, 801, 770, 737, 712, 662  $\text{cm}^{-1}$ .

The Raman spectrum of the product (figure 2) was recorded with the sample in an NMR tube using a Nicolet 960 E.S.P. FT-Raman spectrometer, at 4  $\text{cm}^{-1}$  resolution with excitation from a Nd:V04 laser (1064 nm) with a power output of 400mW. Bands were observed at: 3097, 3070, 2941, 2898, 1750, 1695, 1612, 1584, 1547, 1467, 1443, 1387, 1331, 1315, 1262, 1235, 1213, 1184, 1027, 989, 920, 824, 742, 665, 636, 620, 603, 469, 408, 390, 341, 120, 75  $\text{cm}^{-1}$ .

The X-Ray Powder Diffraction (XRPD) pattern of the product (Figure 3) was recorded using the following acquisition conditions: Tube anode: Cu, Generator tension: 40 kV, Generator current: 40 mA, Start angle: 2.0  $^{\circ}2\theta$ , End angle: 35.0  $^{\circ}2\theta$ , Step size: 0.02  $^{\circ}2\theta$ , Time per step: 2.5 seconds. Characteristic XRPD angles and relative intensities are recorded in Table 1.

**Table 1**

Angle 2-Theta $^{\circ}$	Rel. Intensity %
6.2	2.5
9.0	2.6
13.2	10.0
13.6	11.6
14.6	4.2
14.9	11.0
15.6	5.1
16.6	3.2
17.4	25.9
18.1	47.0
18.6	57.0
18.9	18.2
19.8	5.5
20.6	14.2
21.0	100.0
22.0	12.9



22.9	37.5
23.5	15.5
24.3	10.5
24.7	14.9
25.1	34.4
25.3	25.1
25.9	13.4
26.2	36.2
27.4	24.3
28.4	11.9
28.9	17.8
30.1	14.8
31.4	8.0
31.9	14.1
32.3	15.4
33.5	6.0

The solid-state NMR spectrum of the product (Figure 4) was recorded on a Bruker AMX360 instrument operating at 90.55 MHz: The solid was packed into a 4 mm zirconia MAS rotor fitted with a Kel-F cap and rotor spun at ca.10 kHz. The <sup>13</sup>C MAS spectrum was acquired by cross-polarisation from Hartmann-Hahn matched protons (CP contact time 3 ms, repetition time 15 s) and protons were decoupled during acquisition using a two-pulse phase modulated (TPPM) composite sequence. Chemical shifts were externally referenced to the carboxylate signal of glycine at 176.4 ppm relative to TMS and were observed at: 35.9, 37.8, 49.6, 50.7, 57.1, 64.1, 112.2, 114.6, 121.4, 124.1, 129.5, 132.8, 134.7, 138.9, 143.8, 145.6, 152.7, 157.9, 172.7, 176.5, 179.3 ppm.

#### Properties of the Hydrogensulfate, recorded for the product of Example 2

##### Solid State Stability of the Hydrogensulfate

The solid state stability of the drug substance was determined by storing approximately 1.0 g of the material in a glass bottle at i) 40°C / 75% Relative Humidity (RH), open exposure, for 1 month and b) at 50°C, closed, for 1 month. The material was assayed by HPLC for final content and degradation products in both cases.

a) 40°C / 75% RH: No significant degradation observed (HPLC assay 98% initial).

b) 50°C: No significant degradation observed (HPLC assay 99% initial).

##### T<sub>onset</sub> of the Hydrogensulfate

The T<sub>onset</sub> of the drug substance was determined by Differential Scanning Calorimetry using a Perkin-Elmer DSC7 apparatus.

T<sub>onset</sub> (10°C/minute, closed pan): 184.1°C

**Melting Range of the Hydrogensulfate**

The melting range of the Sulfate was determined according to the method described in the U.S. Pharmacopoeia, USP 23, 1995, <741> "Melting range or temperature, Procedure for Class Ia",  
5 using a Buchi 545 melting point instrument.

Melting range: 183.7 – 188.3°C

10

**CLAIMS**

1. A 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt (the Hydrogensulfate), or a solvate thereof.  
5
2. A compound according to claim 1, characterised by an infrared spectrum substantially in accordance with Figure 1 herein
3. A compound according to claim 1, characterised by a Raman spectrum  
10 substantially in accordance with Figure 2 herein.
4. A compound according to claim 1, characterised by an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3 herein.
- 15 5. A compound according to claim 1, characterised by a Solid State  $^{13}\text{C}$  NMR spectrum substantially in accordance with Figure 4 herein.
6. A 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt, characterised by:  
20 (i) an infrared spectrum substantially in accordance with Figure 1; and  
(ii) a Raman spectrum substantially in accordance with Figure 2; and  
(iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and  
(iii) a Solid State  $^{13}\text{C}$  NMR spectrum substantially in accordance with Figure 4.  
25
7. A compound according to any one of claims 1 to 6, or a solvate thereof, in isolated form.
8. A compound according to any one of claims 1 to 6, or a solvate thereof, in  
30 substantially pure form.
9. A compound according to any one of claims 1 to 6, or a solvate thereof, in crystalline form.
- 35 10. A compound according to any one of claims 1 to 6, or a solvate thereof, in a form having been processed in a manufacturing process requiring or generating heat.
11. A compound according to claim 10, or a solvate thereof, in a bulk form.

- 12 A compound according to claim 10 or 11, or a solvate thereof, wherein the processed form is selected from: a milled form, a heat-dried form, a hot melt processed form and a heat-sterilised form.
- 5
- 13 A compound according to any one of claims 10 to 12, or a solvate thereof, in a milled form.
14. A process for preparing a compound according to any one of claims 1 to 9, or a solvate thereof, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)) or a salt thereof is reacted with a source of sulfate ion; and optionally thereafter as required:
- 10
- (i) forming a solvate thereof;
- (ii) recovering the Hydrogensulfate or solvate thereof ; or
- 15 (iii) further processing the Hydrogensulfate or solvate thereof in a manufacturing process requiring or generating heat.
15. A pharmaceutical composition comprising 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt, (the Hydrogensulfate) or a pharmaceutically acceptable solvate thereof, according to claim 1,
- 20 and a pharmaceutically acceptable carrier therefor.
16. A pharmaceutical composition comprising the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, (the Hydrogensulfate) or
- 25 a pharmaceutically acceptable solvate thereof, according to claim 1, in combination with one or more other anti-diabetic agents and optionally a pharmaceutically acceptable carrier therefor.
17. A pharmaceutical composition according to claim 15 or claim 16, wherein the Hydrogensulfate or the pharmaceutically acceptable solvate thereof, is present in an
- 30 amount providing 1, 2, 4, 8, 12, 4 to 8 or 8 to 12 mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino) ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)).
18. A compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-
- 35 2,4-dione hydrogensulfate salt, or a pharmaceutically acceptable solvate thereof, according to claim 1, for use as an active therapeutic substance.

19. A compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt, or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

5

20. A use of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt, or a pharmaceutically acceptable solvate thereof, according to claim 1, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

10

21. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrogensulfate salt, or a pharmaceutically acceptable solvate thereof, according to claim 1, to a human or non-human mammal in need thereof.

15

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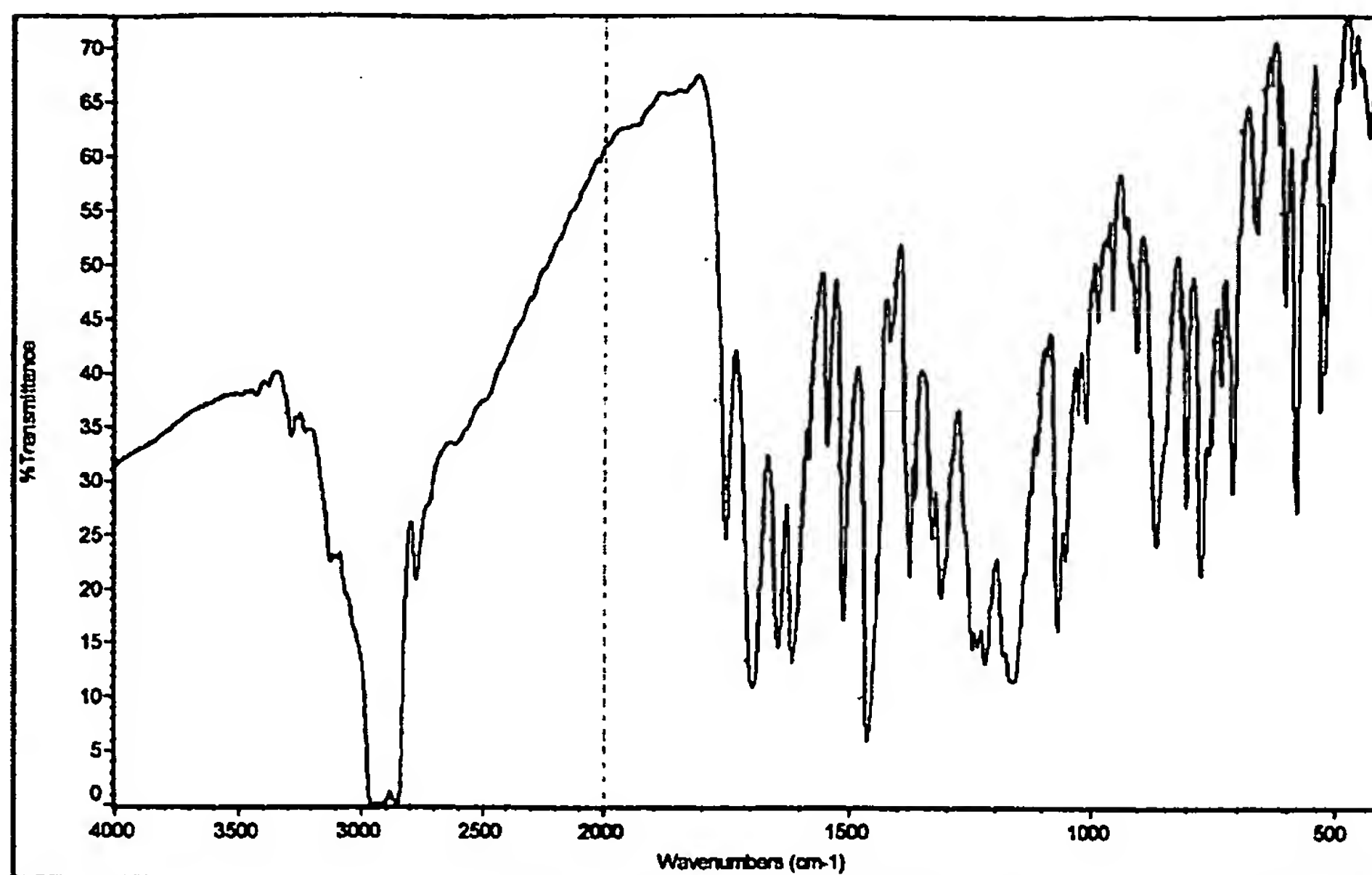
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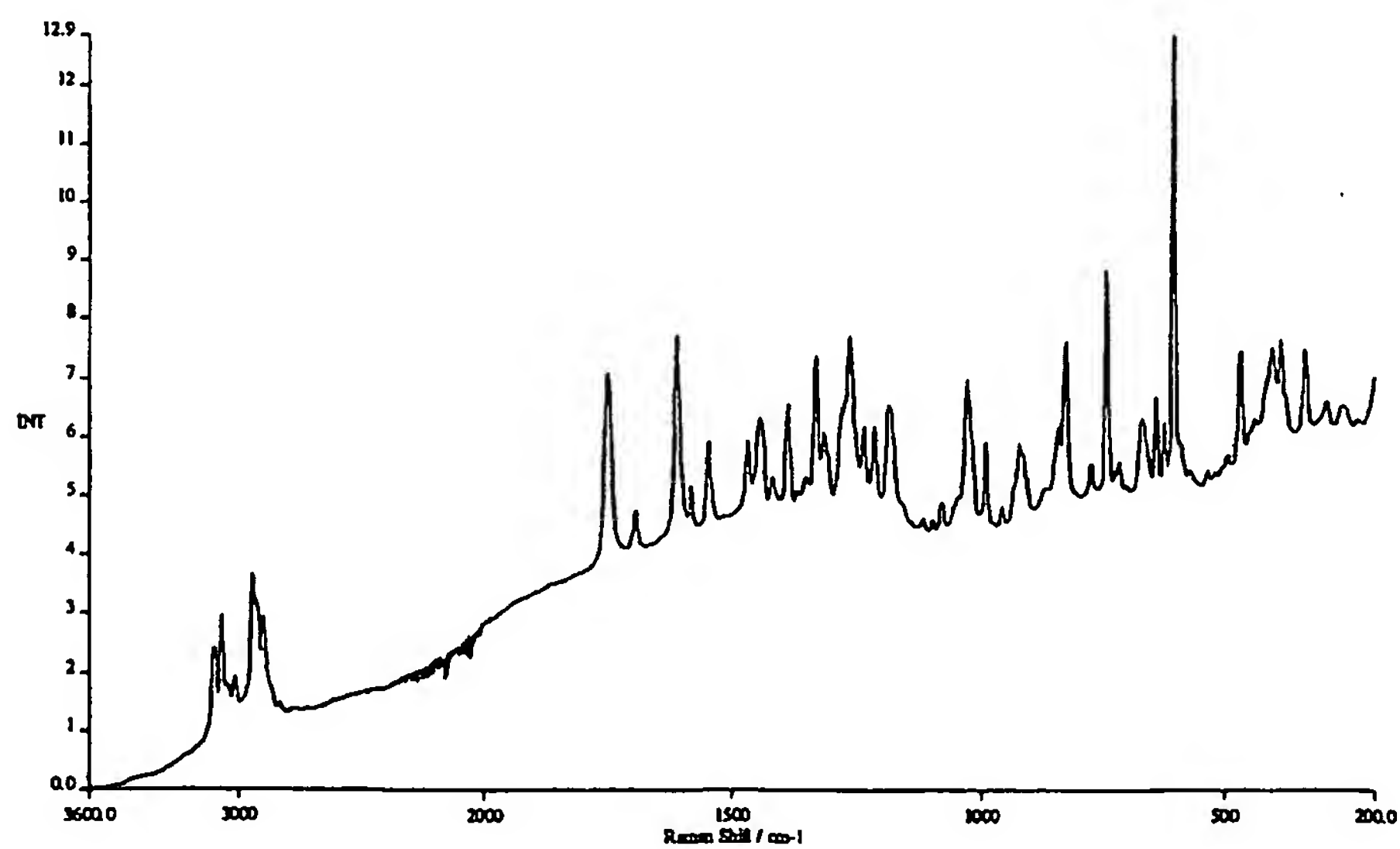


**Figure 1** Infrared spectrum of the Hydrogensulfate



5

**Figure 2** Raman spectrum of the Hydrogensulfate



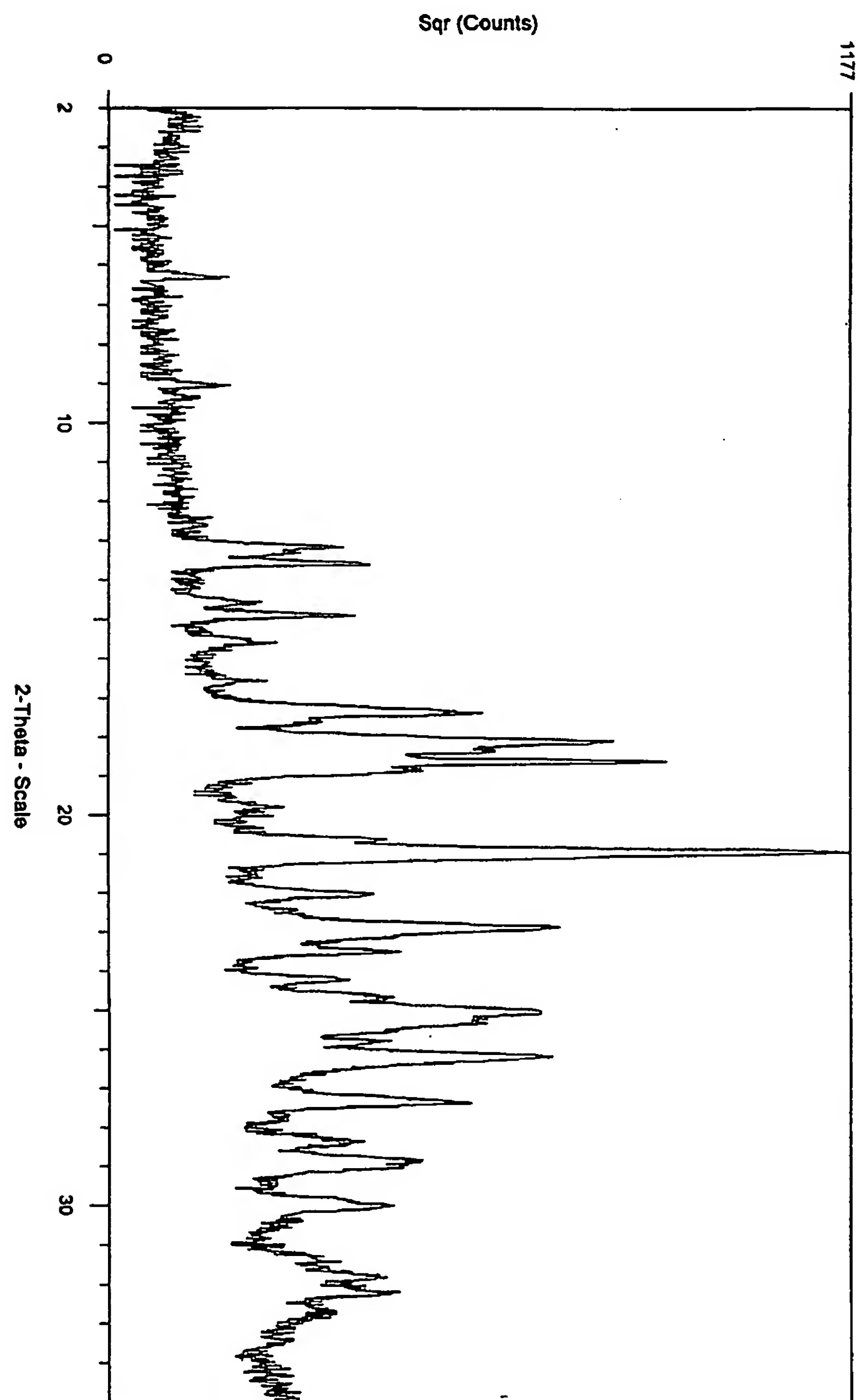
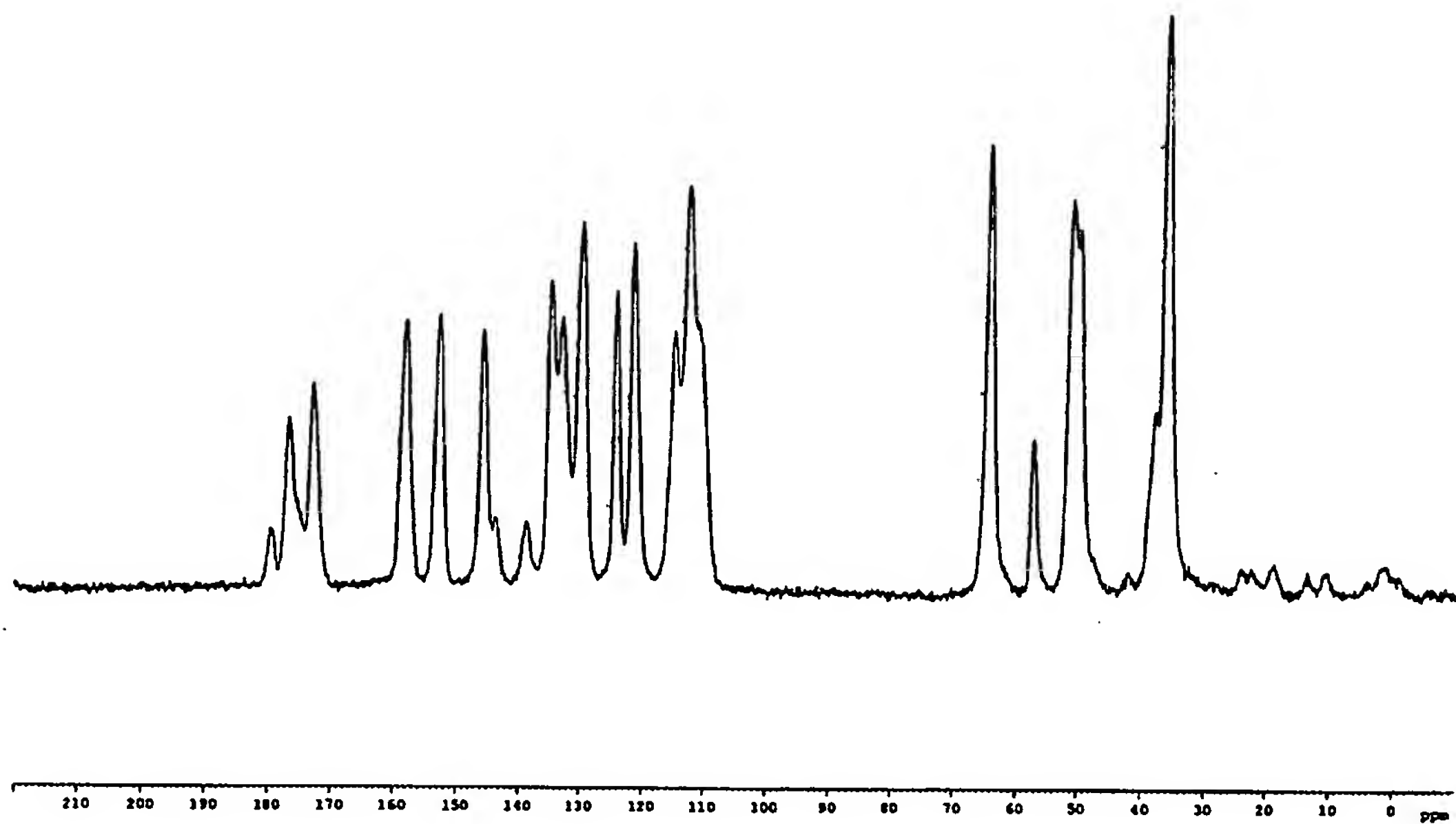
**Figure 3** X-Ray Powder Diffractogram of the Hydrogensulfate

Figure 4 Solid State  $^{13}\text{C}$  NMR spectrum of the Hydrogensulfate



## INTERNATIONAL SEARCH REPORT

International No  
PCT/GB 02/05673

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/12 A61K31/44 A61P3/00 //(C07D417/12,277:00,  
213:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in the application example 30	1
A	WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 (1994-03-17) cited in the application claim 1	1
A	WO 01 44240 A (FISCHER JANOS ;FODOR TAMAS (HU); BALLO ILDIKO (HU); LEVAI SANDOR ( ) 21 June 2001 (2001-06-21) example 1	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*8\* document member of the same patent family

Date of the actual completion of the international search

28 March 2003

Date of mailing of the international search report

10/04/2003

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Bakboord, J

# INTERNATIONAL SEARCH REPORT

International Search Report  
PCT/GB 02/05673

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 31095 A (BLACKLER PAUL DAVID JAMES ;LEE DAVID C (GB); SASSE MICHAEL JOHN (G) 24 June 1999 (1999-06-24) claim 1 ---	1
A	WO 00 63205 A (BLACKLER PAUL DAVID JAMES ;GILES ROBERT GORDON (GB); SASSE MICHAEL) 26 October 2000 (2000-10-26) claim 1 -----	1



# INTERNATIONAL SEARCH REPORT

Internal Application No.  
PCT/GB 02/05673

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 02/05673

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0306228	A	08-03-1989	AT 186724 T	15-12-1999
			AU 2173888 A	09-03-1989
			BR 1100841 A3	20-06-2000
			CA 1328452 A1	12-04-1994
			CA 1339902 A1	09-06-1998
			CZ 9103916 A3	17-03-1993
			DE 3856378 D1	23-12-1999
			DE 3856378 T2	11-05-2000
			DK 490288 A	05-03-1989
			DK 200001556 A	18-10-2000
			EP 0306228 A1	08-03-1989
			EP 0842925 A1	20-05-1998
			ES 2137915 T3	01-01-2000
			GR 3031873 T3	29-02-2000
			HK 1011029 A1	03-11-2000
			JP 10194970 A	28-07-1998
			JP 10194971 A	28-07-1998
			JP 1131169 A	24-05-1989
			JP 2614497 B2	28-05-1997
			JP 2817840 B2	30-10-1998
			JP 9183771 A	15-07-1997
			JP 2837139 B2	14-12-1998
			JP 9183726 A	15-07-1997
			JP 9183772 A	15-07-1997
			KR 164207 B1	15-01-1999
			KR 164275 B1	15-01-1999
			KR 169463 B1	15-01-1999
			LU 90711 A9	05-03-2001
			NZ 226027 A	26-03-1992
			PT 88410 A , B	31-07-1989
			SG 59988 A1	22-02-1999
			SK 391691 A3	11-12-2000
			US 6288095 B1	11-09-2001
			US 5646169 A	08-07-1997
			US 5002953 A	26-03-1991
			US 5521201 A	28-05-1996
			US 5232925 A	03-08-1993
			US 5194443 A	16-03-1993
			US 5756525 A	26-05-1998
			US 5260445 A	09-11-1993
			ZA 8806536 A	26-07-1989
WO 9405659	A	17-03-1994	AP 513 A	30-07-1996
			AT 182147 T	15-07-1999
			AU 674880 B2	16-01-1997
			AU 4973093 A	29-03-1994
			BR 1100916 A3	04-07-2000
			CA 2143849 A1	17-03-1994
			CN 1101911 A , B	26-04-1995
			CN 1183275 A , B	03-06-1998
			CN 1183413 A , B	03-06-1998
			CN 1183276 A , B	03-06-1998
			CZ 9500565 A3	15-11-1995
			CZ 290591 B6	14-08-2002
			DE 69325658 D1	19-08-1999
			DE 69325658 T2	30-12-1999
			DK 658161 T3	29-11-1999
			EP 0658161 A1	21-06-1995

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 02/05673

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9405659	A	EP 0960883 A1	01-12-1999
		ES 2133410 T3	16-09-1999
		FI 951004 A	03-03-1995
		FI 982413 A	06-11-1998
		WO 9405659 A1	17-03-1994
		GR 3030794 T3	30-11-1999
		HK 1012363 A1	05-05-2000
		HU 72639 A2	28-05-1996
		IL 106904 A	30-09-1997
		JP 11147885 A	02-06-1999
		JP 2828777 B2	25-11-1998
		JP 8501095 T	06-02-1996
		JP 2002047288 A	12-02-2002
		LU 90712 A9	12-03-2001
		MX 9305397 A1	31-01-1995
		NO 950852 A	03-03-1995
		NO 974646 A	03-03-1995
		NZ 255505 A	22-08-1997
		PL 307812 A1	26-06-1995
		RU 2128179 C1	27-03-1999
		SG 48302 A1	17-04-1998
		SG 83747 A1	16-10-2001
		SI 9300452 A	30-06-1994
		SK 27795 A3	09-08-1995
		TW 385309 B	21-03-2000
		US 5741803 A	21-04-1998
		US 5910592 A	08-06-1999
		ZA 9306509 A	16-06-1994
WO 0144240	A	21-06-2001	
		HU 9904634 A2	28-01-2002
		AU 2210401 A	25-06-2001
		EP 1242418 A1	25-09-2002
		WO 0144240 A1	21-06-2001
WO 9931095	A	24-06-1999	
		AU 1967999 A	05-07-1999
		BG 104603 A	30-03-2001
		BR 9813600 A	10-10-2000
		CA 2314107 A1	24-06-1999
		CN 1281453 T	24-01-2001
		WO 9931095 A1	24-06-1999
		EP 1040110 A1	04-10-2000
		HR 20000408 A1	31-08-2000
		HU 0100509 A2	29-05-2002
		JP 2002508373 T	19-03-2002
		NO 20003069 A	15-06-2000
		PL 341146 A1	26-03-2001
		SK 9172000 A3	18-01-2001
		TR 9802625 A2	21-10-1999
		TR 200001799 T2	22-01-2001
		US 2002137940 A1	26-09-2002
		ZA 9811506 A	06-11-2000
WO 0063205	A	26-10-2000	
		AU 4130900 A	02-11-2000
		BG 106112 A	31-05-2002
		BR 0009897 A	16-04-2002
		CN 1327447 T	19-12-2001
		CZ 20013759 A3	15-05-2002
		EP 1173436 A2	23-01-2002

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 02/05673

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0063205 A		WO 0063205 A2	26-10-2000
		HR 20010770 A1	31-10-2002
		HU 0200865 A2	28-08-2002
		JP 2002542242 T	10-12-2002
		NO 20015104 A	19-12-2001
		SK 14902001 A3	05-02-2002
		TR 200103040 T2	22-04-2002
<hr/>			